Critical Path Opportunities in OBRR/CBER

CBER Critical Path Workshop

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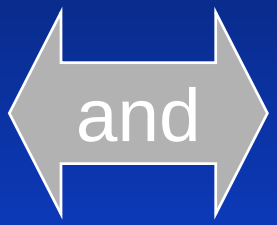
OBRR Product Responsibilities

- **Division of Blood Applications**
  - **Blood and plasma licenses**
  - **Blood establishment software**
  - **Blood grouping reagents**
- **Division of Emerging and Transfusion Transmitted Diseases**
  - **Blood donor screening tests for infectious agents**
  - **Retroviral diagnostics**
- **Division of Hematology**
  - **Bacterial detection devices**
  - **Plasma-derived products (IGIV, albumin, coagulation products)**
  - **Blood and blood component collection devices**
  - **Hemoglobin-based oxygen carrying solutions**

The Critical Path Challenge for Blood Products

Enhance Product Safety, Purity and Potency



Avoid Product Shortages & Major Increased Costs

Critical Path opportunities exist that could improve blood product safety, efficacy and availability while minimizing disruptions to the blood system

Special Role for FDA

- Unique position to identify cross-cutting issues
- Opportunity to coordinate efforts
  - Across the spectrum of blood issues
    - » Product characterization
    - » Safety and efficacy determinations
    - » Supply impacts
  - Across industry functions of developing improved assays and standards
  - Amongst diverse industries involved in manufacturing blood and blood products

Historical Examples of Critical Path Research in OBRR

- 1950's - Stability of albumin
- 1960's - Clotting factor potency
- 1970's - Toxicity of PPF from PKA
- 1980's - HIV safety of plasma fractions
- 1990's - HCV safety of IGIV
- 2000's – Ongoing initiatives
  - » Toxicity of hemoglobin solutions
  - » TransNet model for monitoring blood shortages
  - » Donor screening for West Nile Virus

Critical Path Opportunity: Hemoglobin-Based Oxygen Carriers

Issues

- Blood availability for trauma victims in rural areas and in disaster situations (*e.g.*, war or bioterrorism attack)
- Toxicity of early generation of Hb-based oxygen carrying solutions
  - Vasoconstriction
  - High blood pressure
  - Multiple organ damage

Critical Path Opportunity: Hemoglobin-Based Oxygen Carriers, cont.

Actions

- Identified the link between the “oxidative chemistry” of a given hemoglobin and its toxicity
- Developed Endothelial Cell/Animal-based Model Systems to promote understanding of blood substitute toxicity

Critical Path Opportunity: Hemoglobin-Based Oxygen Carriers, cont.

Outcomes

- Preclinical testing is becoming more predictive of clinical performance
- Design of second generation Hb-based blood substitutes was facilitated

Critical Path Opportunity: Detection of Blood Borne Pathogens

Issue

- Blood safety
  - Need for development of technologies and methodologies that can screen blood donors for a large number of pathogens simultaneously

Critical Path Opportunity: Detection of Blood Borne Pathogens, cont.

Actions

- Develop “multiplex” NAT and DNA microarrays for blood donor screening
- Develop and provide FDA reference panels

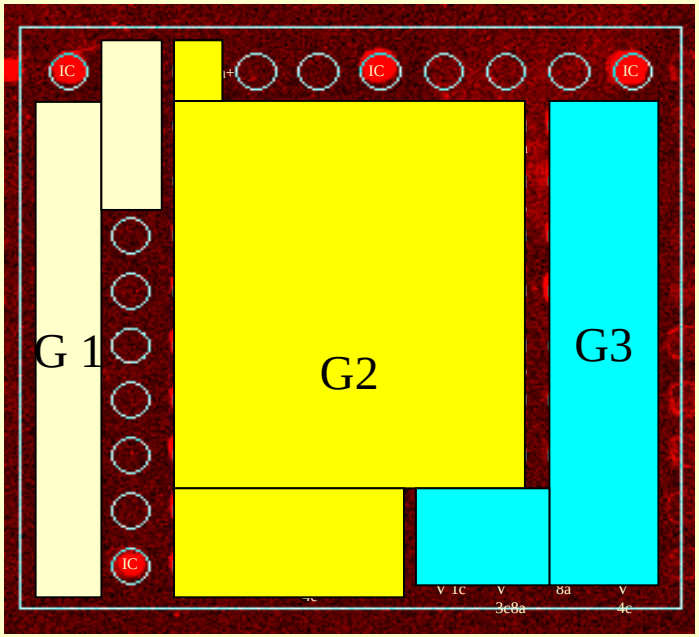
Outcomes

- Identify critical parameters for assay development
- Standardized panels used as a target for industry and to assess different assays
- Reduce the investment costs for industry

Microarray for Detection of Blood-borne and BT Pathogens

Group 1: Bacteria, and Parasites
Ba: *Bacillus anthracis* (**anthrax**)
Ft: *Francisella tularensis* (**tularemia**)
LT: *Leishmania* /*Trypanosoma*
Yp: *Yersinia pestes* and *pseudotuberculosis* (**plague**)

Group 2: Bioterror Viruses
POX: Pox viruses
VAC: Vaccinia
VAR: Variola (**Smallpox**)
MPV: Monkeypox Viruses
CPV: Cowpox Viruses
NOVAC: All Pox viruses but Vaccinia
EBO: Ebola Viruses
VE: Venezuelan Equine Encephalitis Viruses
VETD: VE Trinidad Donkey
MBG: Marburg Viruses



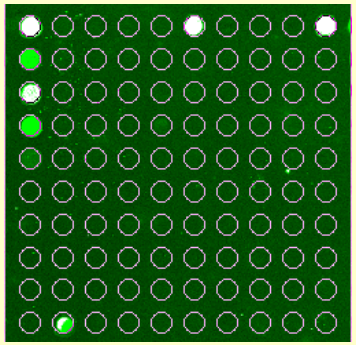
Group 3: Blood Borne Viruses
WNV: West Nile Viruses
HCV: Hepatitis C Viruses
HBV: Hepatitis B Viruses
HIV: Human Immunodeficiency Viruses
HTLV: Human T-cell Leukemia Viruses

IC **4 internal control probes (Human rRNA gene)**

Results of detection in pathogen-spiked blood – 50 cells/ml

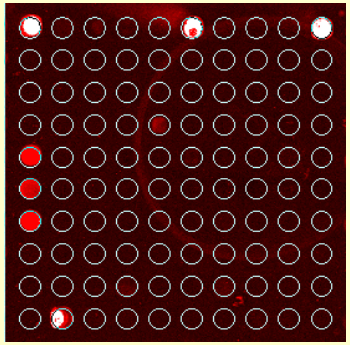
Bacillus anthracis

livestock vaccine strain

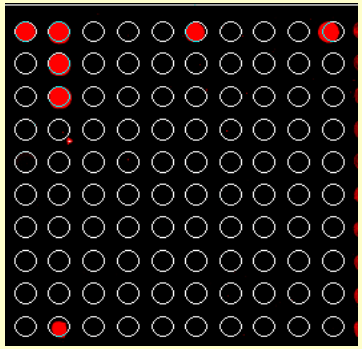


Francisella tularensis

Live Vaccine Strain



Yersinia pseudotub.



Critical Path Opportunity: Counterterrorism – Safety of Smallpox Vaccination

Issue

- Smallpox vaccination can cause life-threatening complications in immunodeficient and eczematous individuals
- Efficacy of Vaccinia immune globulin (VIG) as treatment cannot be tested in humans

Critical Path Opportunity: Counterterrorism – Smallpox Vaccination, cont.

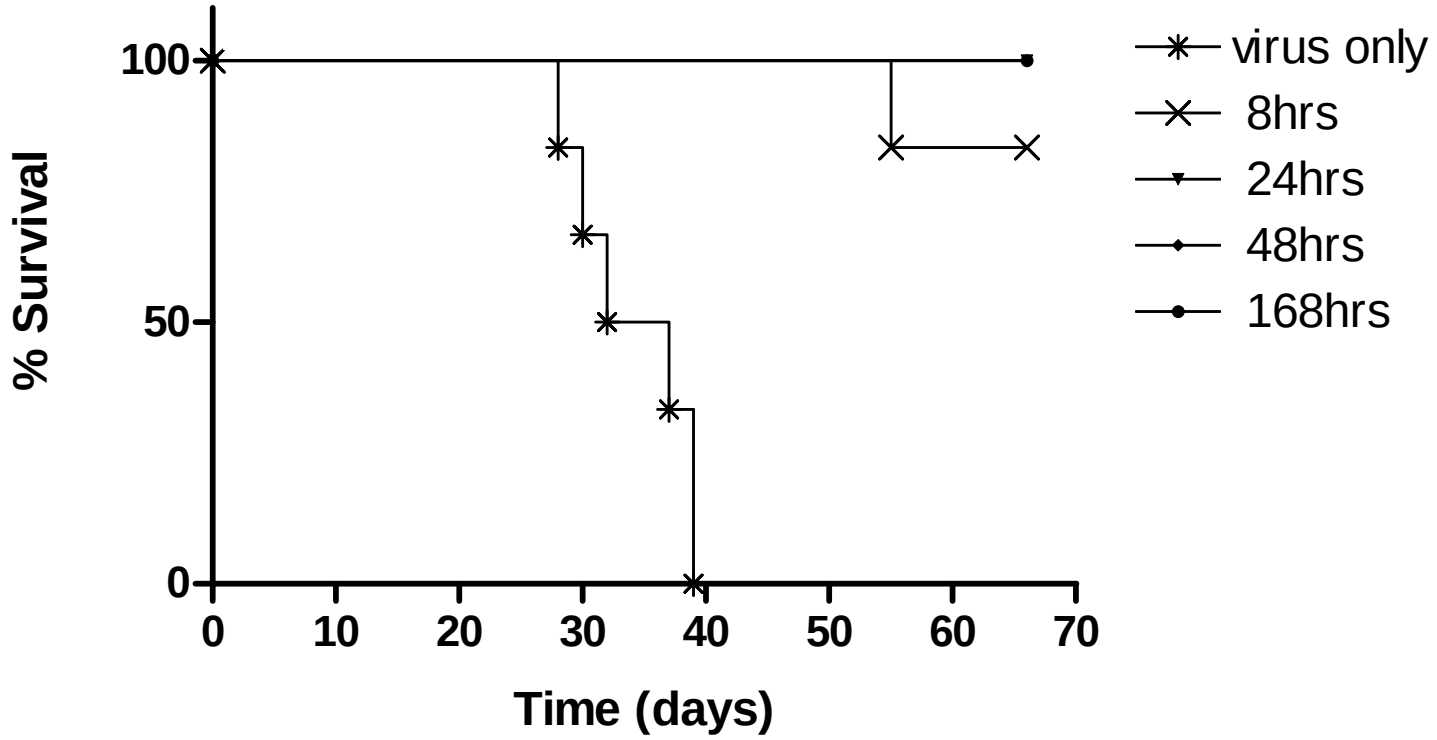
Actions

- Development of a SCID mouse model to test efficacy of VIG

Outcomes

- Transfer of methodology to industry
- Incorporation of this model helps provide a pathway for licensure of new VIGIV products

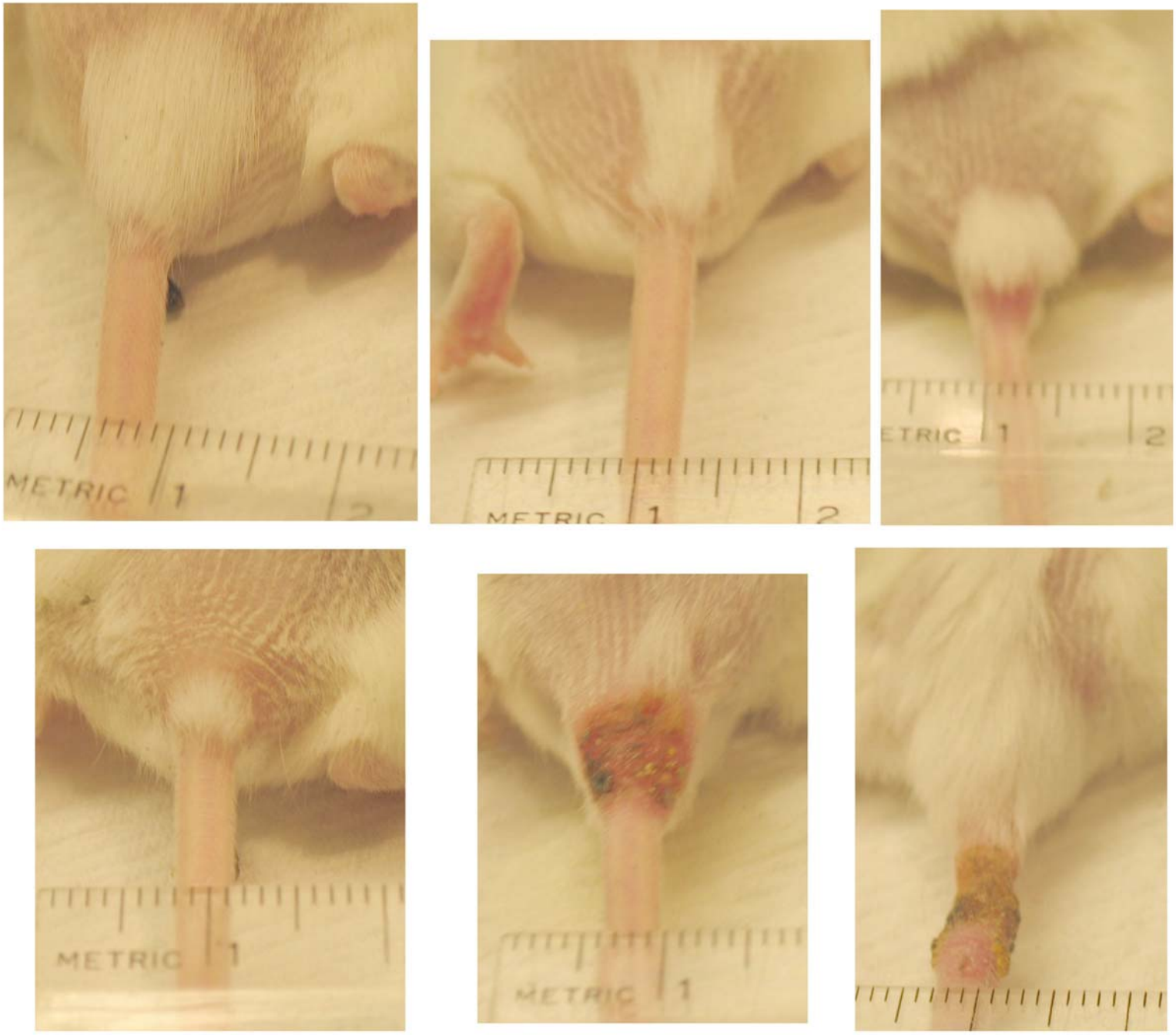
Pre-Exposure Prophylaxis with VIGIV



VIGa at 40mg/mouse

40 mg VIGIV given i.p. to mice at indicated times pre-exposure to 10^6 PFU of vaccinia NYCBOH

Day 40 post-Scarification 10 mg/5 days X 6 Treatment



Critical Path: Potential Initiatives

- Detection of blood-transmissible agents
  - Nucleic acid based test to detect bacteria and parasites in blood
  - Diagnostic and donor screening tests for transmissible spongiform encephalopathies
  - Establishment of cell lines expressing Toll Like Receptors for detecting microbial components in plasma-derived products

Critical Path: Potential Initiatives

- Assessment of Blood Product Safety
  - Animal inoculation studies to evaluate the infectivity of WNV at low titer in blood
  - Animal model to predict immunogenecity of factor VIII products
  - New NAT standards (e.g. parvovirus B19)
- Blood Product Potency
  - Development of an animal model to test function of modified platelets
  - Standards for additional plasma-derived products (e.g., Alpha 1 PI)

Critical Path

OBRR welcomes your ideas!

Thank you.